Amendments to the Specification

Page 1, please replace the paragraph spanning lines 16-28 with the following rewritten paragraph:

Vertebrata have developed myelinated nerve to enable high speed processing of a large amount of information. The myelin sheath, which is characteristic of the myelinated nerve, is formed upon enveloping of nerve axon by cytoplasmic membrane of oligodendrocyte or Schwann cell, and has a multilayer structure. As a result, the nerve becomes insulated as well as acquires an extremely high impedance and extremely low capacitance. The sodium channels are present in accumulation in the nodes of Ranvier, which is a cut line between a myelin sheath and another myelin sheath, and facilitate saltatory conduction of an impulse and enable high speed processing of information (namely, high nerve conduction velocity).

Page 3, please replace the paragraph spanning lines 8-14 with the following rewritten paragraph:

As regards the molecular mechanism of myelination, there is only a report at present that MAG binds with an axon receptor to activate Fyn tyrosine kinase (Umemori H. et al., Nature, 367, p. 572-576 (1994)), and then promotes expression of MBP gene (Umemori H., J. Neurosci., 19, p. 1393-1397 (1999)), which is not sufficient to ~~clear~~ clarify the mechanism.

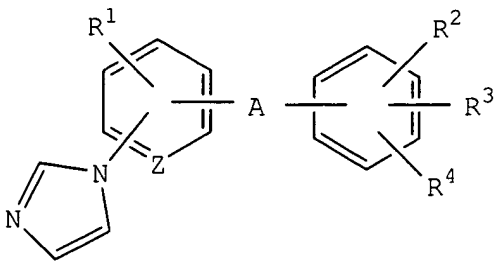
Page 4, please replace the Disclosure of the Invention section spanning line 20 through page 15, line 28 with the following rewritten Disclosure of the Invention section:

Disclosure Of The Invention

The present inventors have conducted intensive studies and found that a compound of the following formula (I), an optically active form thereof and a pharmaceutically acceptable salt thereof promote expression of MAG, and that they are useful as an agent for the prophylaxis and/or treatment of the diseases mainly presenting hypomyelination, and further, dysmyelination or demyelination, which resulted in the

completion of the following invention.

(1) A MAG expression promoter containing a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof (hereinafter sometimes to be generally referred to as the compound of the present invention).

(2) The MAG expression promoter of the above-mentioned (1), which is applicable to a disease of mammals inclusive of ~~human~~ humans, caused by hypomyelination.

(3) The MAG expression promoter of the above-mentioned (1), which is applicable to a disease of mammals inclusive of ~~human, which~~ humans, the disease mainly presents dysmyelination or demyelination.

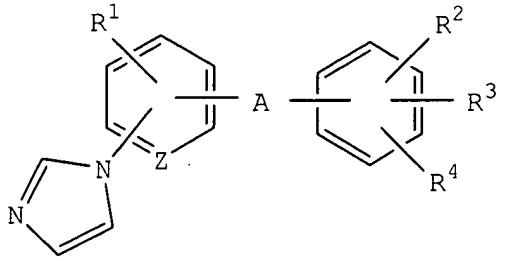
(4) The MAG expression promoter of the above-mentioned (1), which is applicable to a disease of mammals inclusive of ~~human, which~~ humans, the disease being multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic

inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease.

(5) The MAG expression promoter of any of the above-mentioned (1) to (4), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(6) A MAG expression promoter comprising 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof.

(7) A method of promoting expression of MAG, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

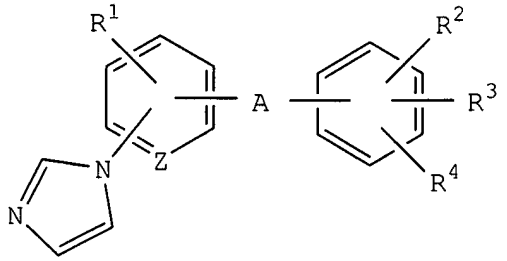
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of ~~human~~ humans.

(8) The method of the above-mentioned (7), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(9) A method for promoting expression of MAG, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of ~~human~~ humans.

(10) A method for prophylaxis and/or therapy of a disease caused by hypomyelination, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

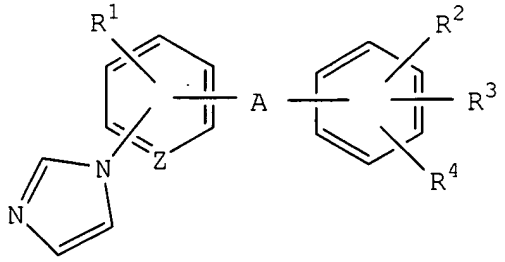
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of ~~human~~ humans.

(11) The method of the above-mentioned (10), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(12) A method for prophylaxis and/or therapy of a disease caused by hypomyelination, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of ~~human~~ humans.

(13) A method for prophylaxis and/or therapy of a disease mainly presenting dysmyelination or demyelination, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

Z is =CH- or =N-,

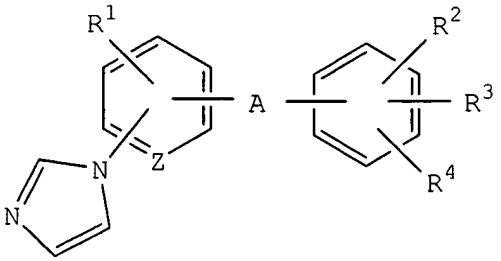
an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of ~~human~~ humans.

(14) The method of the above-mentioned (13), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(15) A method for prophylaxis and/or therapy of a disease mainly presenting dysmyelination or demyelination, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of ~~human~~ humans.

(16) A method for prophylaxis and/or therapy of multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy

metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease, which method comprises administering a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

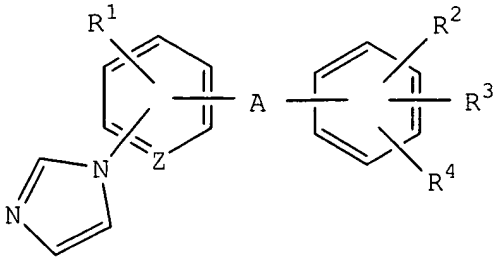
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of ~~human~~ humans.

(17) The method of the above-mentioned (16), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(18) A method for prophylaxis and/or therapy of multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease, which method comprises administering 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof to mammals inclusive of ~~human~~ humans.

(19) Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

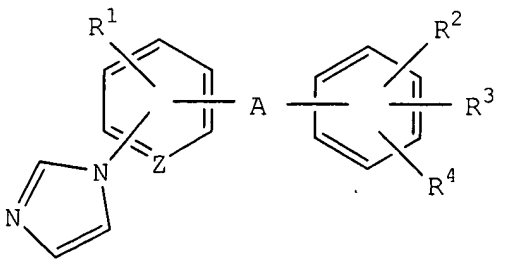
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter.

(20) The use of the above-mentioned (19), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(21) Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter.

(22) Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, $-COOR^5$, $-CONR^6R^7$, $-CH_2NR^6R^7$, $-CH_2OH$ or $-CH_2OR^8$;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

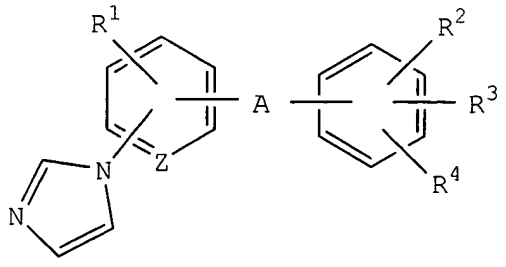
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of ~~human~~ humans, which is caused by hypomyelination.

(23) The use of the above-mentioned (22), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(24) Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of ~~human~~ humans, which is caused by hypomyelination.

(25) Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a

hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, -$COOR^5$, -$CONR^6R^7$, -$CH_2NR^6R^7$, -CH_2OH or -CH_2OR^8;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or -CH_2-; and

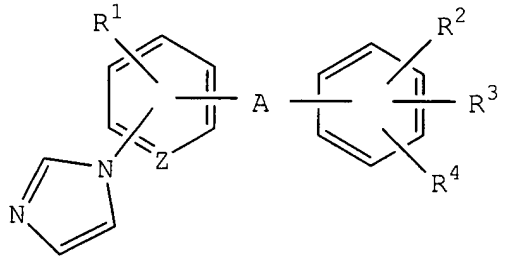
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of ~~human~~ humans, which mainly presents dysmyelination or demyelination.

(26) The use of the above-mentioned (25), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(27) Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of ~~human~~ humans, which mainly presents dysmyelination or demyelination.

(28) Use of a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, -$COOR^5$, -$CONR^6R^7$, -$CH_2NR^6R^7$, -CH_2OH or -CH_2OR^8;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or $-CH_2-$; and

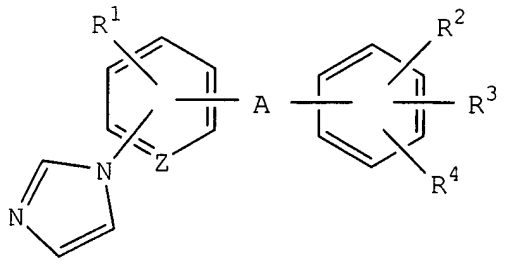
Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of ~~human~~ humans, which is multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease.

(29) The use of the above-mentioned (28), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(30) Use of 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof for producing a MAG expression promoter applicable to a disease in mammals inclusive of ~~human~~ humans, which is multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration or Charcot-Marie-Tooth disease.

(31) A commercial package comprising a MAG expression promoter comprising a compound of the formula (I)



(I)

wherein

R^1 is a hydrogen atom, a halogen atom, an alkyl group or an alkoxy group;

R^2 and R^3 are the same or different and each is a

hydrogen atom or an alkyl group;

R^4 is an alkyl group, -COOH, -$COOR^5$, -$CONR^6R^7$, -$CH_2NR^6R^7$, -CH_2OH or -CH_2OR^8;

wherein R^5 and ~~R^6~~ R^8 are each an alkyl group, and R^6 and R^7 are the same or different and each is a hydrogen atom or an alkyl group, or R^6 and R^7 in combination form imidazole together with the adjacent nitrogen atom;

A is -CH(OH)-, -C(=O)- or -CH_2-; and

Z is =CH- or =N-,

an optically active form thereof or a pharmaceutically acceptable salt thereof and a written matter associated therewith, the written matter stating that the MAG expression promoter can or should be used for promoting expression of MAG.

(32) The commercial package of the above-mentioned (31), wherein, in the formula (I), R^1 is a halogen atom, an alkyl group or an alkoxy group.

(33) A commercial package comprising a MAG expression promoter comprising 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, an optically active form thereof or a pharmaceutically acceptable salt thereof and a written matter associated therewith, the written matter stating that the MAG expression promoter can or should be used for promoting expression of MAG.

Page 16, please replace the paragraphs spanning line 18 through page 17, line 2 with the following rewritten paragraphs:

The MAG expression promoter of the present invention encompasses any such promoter as long as it can promote in vitro or in vivo expression of MAG at a gene level or a protein level.

The disease caused by hypomyelination is a disease of mammals inclusive of ~~human~~ humans, including any disease mainly presenting the disease state of hypomyelination, dysmyelination or demyelination.

Moreover, the disease mainly presenting dysmyelination or demyelination means diseases of mammals inclusive of ~~human~~ humans, and encompasses any disease mainly presenting the disease state of hypomyelination, dysmyelination or demyelination. Examples thereof include multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis,

diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration, Charcot-Marie-Tooth disease and the like.

Page 18, please replace the paragraph spanning lines 6-19 with the following rewritten paragraph:

The compound of the present invention can be used as an active ingredient of a MAG expression promoter for promoting the expression of MAG in mammals such as a human, cow, horse, dog, mouse, rat and the like. Therefore, the compound of the present invention is useful as an agent for the prophylaxis and/or treatment of diseases mainly presenting hypomyelination, further, dysmyelination or demyelination, particularly as an agent for the prophylaxis and/or treatment of multiple sclerosis, encephalitis, myelitis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis, hypothyroidism, metachromatic leukodegeneration and Charcot-Marie-Tooth disease.

Page 20, please replace the paragraph spanning lines 16-29 with the following rewritten paragraph:

When a solid preparation is produced, additives are used. Examples of the additive include sucrose, lactose, cellulose, D-mannitol, maltitol, dextran, starch, agar, ~~arginate~~ alginate, chitin, chitosan, pectin, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, calcium phosphate, sorbitol, glycine, carboxy methylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, glycerin, polyethylene glycol, sodium hydrogencarbonate, magnesium stearate, talc and the like. Tablets can be prepared into those applied with general coating as necessary, such as sugar-coated tablets, enteric coated tablets and film coated tablets. Moreover, two-layer tablets and multi-layer tablets can be prepared.

Page 28, please replace the paragraph spanning lines 18-30 with the following rewritten paragraph:

The MAG expression promoter of the present invention is useful as an agent for the prophylaxis and/or treatment of diseases mainly presenting hypomyelination, and further, dysmyelination or demyelination. More particularly, it is useful as an agent for the prophylaxis and/or treatment of diseases of mammals inclusive of ~~human~~ humans, such as multiple sclerosis, encephalitis, myelitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculitis, heavy metal toxicosis, diphtheria toxicosis,

hypothyroidism, metachromatic leukodegeneration, Charcot-Marie-Tooth disease and the like.

Amendments to the Abstract

Kindly replace the Abstract as set forth on the attached separate sheet.